10. The method according to claim 9, wherein said growth factor is selected from the group consisting of fibroblast growth factor, vascular endothelial growth factor, transforming growth factor beta, platelet-derived growth factor, and granulocyte-macrophage colony-stimulating growth factor.

11. The method according to claim 1, wherein said gene encodes a chemikine.

12. The method according to claim 11, wherein said chemikine is selected from the group consisting of monocyte chemoattractant protein-1, macrophage inflammatory protein-1 and -2, and cytokine induced neutrophil chemoattractants.

REMARKS

Claims 1-7 are pending in the application. All claims stand rejected. The applicants request reconsideration of the rejections in the light of the claim amendment and the following remarks.

New claims 8-12 have been added. These recite the genes that can be incorporated into glomeruli by the inventive method, and are disclosed in paragraph [014] of the specification.

Declaration

The examiner requires a new Declaration of Inventorship on an allegation that the declaration as filled has been altered without dating and initializing the alteration. The applicants contend that a re-submission is not called for.

The applicant argues that the substance of the Declaration has not been altered. The only alteration appears in the wording of the boiler plate form itself, wherein the word "provisional" was inserted in the form merely to identify the priority application whose serial number followed on the form.

Rejections under 35 USC 112(2nd)

The examiner rejects all pending claims on an allegation that the phrase "an effective amount of adenoviral vector" in claim 1 is indefinite because "it is unclear what constitutes an 'effective amount', and that "effective period of time" and "effectively slow rate" are also indefinite. The applicant traverses this rejection.

The Court of Customs and Patent Appeals, the forerunner of the Federal Circuit has held that "A broad definition of a quantity or dosage are(*sic*) not indefinite where the invention resides in the finding of the activity, rather than in discovering some critical range or the like" *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). The same court later held that "[C]ompliance with the written description of Section 112 only requires that appellant's application contain sufficient disclosure, expressly or inherently, to make it clear to persons skilled in the art that appellant possessed the subject matter claimed". *In re Mott* 539 F.2d 1291, 190 USPQ 536,541 (CCPA 1976). The Federal Circuit later held that "The test for determining compliance with the written description requirement is whether the disclosure of the application...reasonably conveys to the artisan that the inventor had possession of the claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language." *In re Kaslow* 707 F.2d 1366, 217 USPQ 1089, 1096 (Fed. Cir. 1983). As to the need for some experimentation in order to practice the invention, the Federal Circuit found that a patent is not invalid because of a need for mere experimentation to practice the invention. W.L. Gore & Associates, Inc. v Garlock, Inc. 220 USPQ 303 (Fed. Cir. 1983).

It is clear that neither the law nor the specification and claims support the examiner's position. A list of the disclosures will make this clear:

1. Claim 1 recites the limitation that the effective conditions are those that produce vector infection in <u>at least 30%</u> of the glomerular cells. This provides an important

limitation. The examiner accepts such a definition of "effective amount" in the Sukhatme reference ('230 patent) cited by him (see column 5, lines 26-43).

2. Paragraph [022] provides a range of effective amounts of the vector.

3. Table 1 shows typical doses of the vector.

4. Paragraphs [032] and [035] in Example 3 show a typical dosage of the vector particles.

5. Paragraph [037] and [039] in Example 4 provide effective dosages of the vector.

6. Paragraph [042} in Example 5 describes still additional effective amounts of the viral vector.

7. Lines 2 and 3 on specification page 11 provide the range of effective times for the infusions of the adenovirus.

8. Examples 2-4 provide information as to how long after *in vivo* infusion positive results will appear.

The applicant submits that the specification provides all the definiteness necessary under current law for claim 1. Therefore, all rejections under 112(2nd) should be withdrawn.

<u>Rejection under 35 USC 112(1st)</u>

The examiner rejects claim 2 on an allegation that the specification does not disclose control elements. The applicants traverse this rejection.

Paragraph [014] of the specification provides in great detail the specific enhancer and gene promoter used in the reduction to practice of the invention. Paragraph [014] of the specification describes suitable control elements. The level of skill in this art is very high. It will be abundantly clear to the artisan to whom this patent application is addressed how to use suitable control elements. These are well known in the art and, as such, need not be referenced.

It would be appropriate for the examiner to withdraw this rejection.

Additional rejections under 35 USC 112(1st)

The examiner rejects claims 1-7 as being nonenabled by the specification, for a variety of reasons. These will be traversed *in seriatum*.

Effective amount

The examiner again claims that "effective amount" is not enabled. Applicant submits that this argument was appropriately addressed above.

Breadth

The examiner argues that the breadth of the claims is too broad, and that they would encompass any species of mammal, including animals and humans, and that the claims would encompass "treating any disorder associated with the kidney."

First, the examiner is reminded that applicants claim a method for gene transfer specifically into glomerular cells, not all cells of the kidney, thus limiting the diseases that could possibly be treated by their technique. Further, the expression "requiring same" is no longer present in amended claim 1, mooting any consideration of a specific disease.

Second, the applicants describe gene transfer into glomerular cells of a "mammalian subject" in general and, as the examiner acknowledges, applicant has demonstrated specific gene transfer into glomerular cells of two species of mammal; this is sufficient to support the claims.

Third, quoting again a CCPA case, " [C]laims to methods of producing antidepressant activity which comprises internally administering certain compounds are not indefinite, although there is no reference to a host, since it is made clear that compounds would find their primary use as medication for humans with the possibility that they might find some veterinary use in other animals" *In re Gardner, supra.* This court did not even require that the specification mention a specific mammalian host; applicant has exceeded that standard by demonstrating gene transfer into cells of <u>two</u> species of mammals.

<u>Unpredictability of the art</u>

The examiner expounds at length on the assumed unpredictability of gene therapy as a whole, and makes an unsupported leap to a conclusion that, for this reason, the applicants' claimed method could not have clinical success. The applicants have discovered a method of specifically inserting a gene into glomerular cells, and have demonstrated this in human cells, as well as rat cells. This is all that is needed to support the claim. Clinical trials in humans are required by the FDA, not by the USPTO. More importantly, applicant is not claiming a method for gene therapy, simply a method for gene transfer into a specific cell type.

Even if applicant was claiming a method for specific gene therapy, it might be instructive to note that the examiner quotes from a <u>1995</u> (not 2000) Science article by Crystal to make his point. Considering the state of the art in gene therapy, Crystal also says in the Abstract of this 1995 article: "[E]nough information has been gleaned from clinical trials to allow the conclusion that human gene transfer is feasible, can evoke biologic

responses that are relevant to human disease..." As concrete evidence that the USPTO recognizes gene therapy methods as patentable, the applicants' undersigned attorney made a cursory computer search of the PTO's data base of issued patents in this field beginning in 2000, and easily found many issued patents that included gene therapy in their titles and contents, each involving gene therapy in mammalian subjects and none involving human trials, *e.g.*, 6410015, 638757, 6375929, 6372250, 6350444, 6335112, 6331528, 6287557, 6271211, 6218180, 6204251, 6174841, and 6150338. Methods for gene transfer, which is the subject matter of applicant's invention, have been the subject of US patents, too numerous to list.

Working examples

The examiner asserts that the applicants have not provided an example of treating a specific human disease/disorder using an adenoviral vector. The applicants submit that this is not required for patentability of claims 1-7, as amended.

It is established law that 35 USC 112 requires nothing more than objective enablement; how such a teaching is set forth, either in the use of illustrative examples or by broad terminology is of no importance. *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367, 369 (CCPA 1971). This review was reaffirmed by the CCPA in *In re Strahlivitz*, 212 USPQ 561 (CCPR 1992) and the Federal Circuit in *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). In the present case, objective enablement of the claims is provided, not only broadly by the specification (see, specifically, paragraphs [006]-[011], [016] and [026]), but also specifically by the working *in vivo* and *in vitro* examples 1-5.

Further, applicant is not claiming a method for treating a specific glomerular disease.

Quantity of experimentation

The examiner then argues that bringing this invention into clinical use would involve years of effort, including clinical trials. As applicants stated above, the law does not require an applicant to wait until an inventive method is approved for clinical use in order to obtain a patent on the method. The method of claim 1 satisfies all of the requirements for patentability: it is useful; it is novel; it is unobvious; and satisfies the 112 requirements. The applicants are entitled to a finding of patentability.

Rejection under 35 USC 102(b)

Oddly, the examiner has premised his 102(b) rejection of claims 1 and 3-7 over Sukhatme USPN 5,869,230 on his rejection under 112(1st) discussed above. The applicants, being uncertain as to the examiner's theory for rejection, will traverse the 102(b) rejection as though it was standing alone.

In deciding the issue of anticipation, the examiner must identify all of the elements of the claims, determine their meaning in light of the specification and prosecution history, and identify corresponding elements disclosed only in the allegedly anticipating reference, and no other. *Lindemann Maschinenfabrik v. American Hoist and Dairy Co.*, 730 F.2d 1452, 1458, 221 USPQ 481, 485-86 (Fed. Cir. 1984); *Richardson v. Suzuki Motor Co.*, 868 F. 2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir.1989), *cert. den.* 110 S. Ct. 154 (1989).

A key element in claim 1 of the present invention is that the cells into which the gene is transferred are kidney glomerular cells . The examiner errs in stating that Sukhatme demonstrated gene transfer into renal glomerular cells. To the contrary, this reference relates only to endothelial cells of the inner and outer medulla, not glomerular cells (see Sukhatme Abstract, line 12; column 5, line 40; and, Sukhatme claim 1). Further, as noted on page 2, line 11 of the present specification, Sukhatme's technique did not result in any gene transfer into glomerular cells (see Zhu *et al,, Gene Therapy* 3:298(1996), of record, p.

299; Sukhatme '230 patent, col. 17, lines 52-53 ("...glomeruli and glomerular capillary loop were not stained.")). For this reason alone, Sukhatme '230 patent does not qualify as 102(b) prior art.

There is yet another reason why Sukhatme is not valid as anticipatory prior art. The method disclosed by this reference requires infusing the virus and incubating the virus with the kidney for a period of time (up to 45 minutes), which results in low levels of infection. In sharp contrast, in the applicants' successful method the virus needs to be actively passing through the kidney to achieve efficient infection. The relevant present claim element relating to this feature is "...infusing... continuously... in a single pass...", which discloses that the kidney was infused continuously with the virus, in contrast to Sukhatme's static incubation method. For this reason also, Sukhatme fails as a 102(b) reference. It should also be noted that in Sukhatme's method, a vasodilator is present during infusion; this is not done in the present method.

Conclusion

All claims are deemed by the applicants to be allowable. Accordingly, the examiner is respectfully requested to withdraw all objections and rejections, and pass this application to issue.

Respectfully submitted,

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CLEAN COPY OF CLAIMS

1. A method of infecting the glomerular cells of a kidney of a mammalian subject with a recombinant adenovirus vector carrying a gene or genes of interest, comprising the step of infusing intra-renal arterially and continuously in a single pass through the superior mesenteric artery or renal artery an effective amount of said adenoviral vector into said kidney at an effectively slow rate over an effective period of time, under conditions such that at least 30% of said glomerular cells are infected with said vector.

2. The method according to claim 1, wherein said adenovirus vector carries a control element that preferentially expresses said gene or genes into renal glomerular cells.

3. The method according to claim 1, wherein said kidney is maintained at reduced temperatures during said infusion procedure.

4. The method according to claim 1, further comprising clamping the aorta above and below said superior mesenteric renal artery of said kidney, and infusing through said superior mesenteric renal artery.

5. The method according to claim 1, wherein said renal artery is cannulated directly without clamping of said aorta during said infusion.

6. The method according to claim 1, wherein said mammal is a rodent, said rate of infusion is about 0.1- 0.5 x 10^{11} particles per minute, and said effective period of adenoviral vector infusion is between about 15 and 120 minutes.

7. The method according to claim 1, further comprising concurrent cannulation of the femoral vein through the vena cava into the renal vein so as to direct vector not taken up by renal glomerular cells away from the general circulation.

8. The method according to claim 1, wherein said gene is the lacZ gene.

9. The method according to claim 1, wherein said gene encodes a growth factor.

10. The method according to claim 9, wherein said growth factor is selected from the group consisting of fibroblast growth factor, vascular endothelial growth factor, transforming growth factor beta, platelet-derived growth factor, and granulocyte-macrophage colony-stimulating growth factor.

11. The method according to claim 1, wherein said gene encodes a chemikine.

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12. The method according to claim 11, wherein said chemikine is selected from the group consisting of monocyte chemoattractant protein-1, macrophage inflammatory protein-1 and -2, and cytokine-induced neutrophil chemoattractants.